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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/819,097	03/05/2001	Andrea Margaret Douglas	11375Z	6127

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EXAMINER
DEBERRY, REGINA M

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 02/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/819,097	DOUGLAS ET AL.	
	Examin r	Art Unit	
	Regina M. DeBerry	1647	

-- Th MAILING DATE of this communication app ars on the cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-42* is/are pending in the application.

4a) Of the above claim(s) *26-29 and 37-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *30-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *26-42* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9,10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Status of Application, Amendments and/or Claims

The amendment filed 23 May 2001 (Paper No. 8) has been entered in full. Claims 21-25 were cancelled.

The information disclosure statements filed 10 January 2002 (Paper No. 9) and 12 April 2001 (Paper No. 10) were received and comply with the provisions of 37 CFR §§1.97 and 1.98. They have been placed in the application file and the information referred to therein has been considered as to the merits. The Applicant's attention is directed to the PTO-1449 forms (Paper No. 9 and Paper No. 10) which cite identical references (Douglas *et al.*, Int. J. Cancer, 75/1:64-73, 1998 and Douglas *et al.* Oncogene 14/6:661-669, 1997).

The amendment filed 15 April 2002 (Paper No. 11) has been entered in full. Claims 1-20 were cancelled. New claims 30-42 were added.

Applicant's election with traverse of Group II (claims 30-36) and species election of oncostatin M (OSM) in Paper No. 14 is acknowledged. The traversal is on the grounds that the Groups I and II are not independent and distinct but are different aspects of a single invention. Applicant cites 35 USC 112. Applicant states that the classification of the groups of claims does not establish independence and distinctness. Applicant discusses the cost of fees and potential limitation of financial resources. Applicant states that patents issuing on divisional applications which are filed to prosecute claims that the Examiner held to be independent and distinct can be vulnerable to legal challenges alleging double patenting. Applicant cites case law. Applicant states that the courts affirmed the invalidation on double patenting grounds of

a patent that had issued from a divisional application filed following a restriction requirement.

Applicant's arguments have been considered but are not deemed persuasive. Applicant's attention is directed to MPEP 806.05. Where two or more related inventions are being claimed, the principle question to be determined in connection with a *requirement to restrict or a rejection on the grounds of double patenting* is whether or not the inventions as claimed are distinct. If they are distinct, restriction may be proper. If they are not distinct, restriction is never proper. Various pairs of related inventions are noted in sections 806.05(a)-(i). Groups I and II fall under 806.05(h) Product and Process of Using. The burden is on the Examiner to provide an example, but the example need not be documented. If the Applicant either proves or provides a convincing argument that the alternative use suggested by the Examiner cannot be accomplished, the burden is on the Examiner to support a viable alternative use or withdrawn the requirement. The Examiner has provided an example in the Election/Restrictions (17 June 2002 Paper No. 12). The Applicant has not provided a convincing argument that the alternative use suggested by the Examiner cannot be accomplished.

Applicant's attention is also directed to MPEP 808.02. Where the related inventions as claimed are shown to be distinct under the criteria of MPEP 806.05(c)-(i), the Examiner, in order to establish reasons for insisting upon restriction, must show by appropriate explanation one of the followings: Separate classification thereof, separate status in the art when they are classifiable together or a Different field of search. The Examiner has shown a different classification in the Election/Restrictions (17 June 2002

Paper No. 12). Furthermore, while examination may possibly require a search of classes that overlap there is no reason to believe that the search would be co-extensive. Lastly, while the added cost to the Applicants to file divisional applications is truly regretted, it is beyond the resources of the USPTO to permit examination of multiple inventions in a single application.

The requirement is still deemed proper and is therefore made FINAL. Claims 26-29, 37-42 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 14.

Claim Objections

Claims 30 and 33-36 are objected to because of the following informalities: The instant claims encompass non-elected inventions (species) and require amendment to limit to elected invention. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Appropriate correction is required.

Specification

The disclosure is objected to because of the following informalities:

In the Brief Description of the Drawings (Figure 9, page 21, lines 4 and 7), a reference is incorrectly made to Figure 10(a) and Figure 10(b). Appropriate correction is required.

On pages 40-41 (Table 2), the meaning of the superscript at the end of each sequence is unclear and barely visible. It is suggested that Applicant add a notation in Table 2 directing attention to the number recited at the end of the sequence as a referenced SEQ ID NO: For example, "The superscript number at the end of each sequence represents the SEQ ID NO:"

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 30-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The instant claims are generally drawn to a method of inhibiting the proliferation of malignant breast cancer cells in a mammal, said method comprising administering to said mammal an effective amount of oncostatin M (OSM) for a time and under conditions sufficient to ameliorate the effects of or to delay onset of breast cancer in a mammal.

One cannot extrapolate the teaching of the specification to the claimed invention because there is no guidance on or exemplification of any correlation between inhibiting proliferation of a breast cancer line in the presence of OSM (*in vitro*) and administering OSM to a mammal to inhibit the proliferation of malignant breast cancer cells (*in vivo*).

The *in vitro* experimental data presented is clearly not drawn to subjects with breast cancer. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, pg 4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant in vitro but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Dermer (Bio/Technology, March 1994, Vol.12, No. 3 pg. 320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. In addition, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary -type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

It is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second paragraph). Because of the known unpredictability of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the method comprising the administration of OSM, would function as claimed based only upon the known mechanism of action of OSM in cell culture. Further, the refractory nature of cancer to drugs is well known in the art.

Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited. Curti further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging

pages 29-30). He concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2).

Hartwell *et al.* (Science, 1997, 278:1064-1068) teach that an effective chemotherapeutic must selectively kill tumor cells, most anticancer drugs have been discovered by serendipity, the molecular alterations that provide selective tumor cell killing are unknown and that even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (pg.1064-1065). Jain (cited supra) specifically teaches that systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells (p. 58, col 2, paragraph 2).

Anti-tumor agents and those that prevent, reduce, retard or eliminate secretion of metastatic promoters, must accomplish several tasks to be effective. They must be delivered into the circulation that supplies the tumor or metastatic promoter producing cells. They must interact at the proper site of action (selective for tumor cells) and must do so at a sufficient concentration and for a sufficient period of time. It is clear, as disclosed above that the specification does not teach how to make/use a formulation with a targeting molecule. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The formulation may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half life of the formulation. In addition, the formulation may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted,

may be absorbed by fluids, cells and tissues where the formulation has no effect, circulation into the target area may be insufficient to carry the formulation and a large enough local concentration may not be established.

In addition, claim 30 recites the limitations "delay onset" and "ameliorate the effects". This would also require administration to a subject in order to discern whether the effects of breast cancer have been ameliorated. This would also require administration of the claimed invention prior to the development of the tumors. However, there is no guidance in the specification for determining the appropriate time prior to the development of tumors to begin the therapy or for identifying patients at risk for developing those tumors. There is no guidance to what effects are being examined.

The specification provides insufficient guidance with regard to the issues raised above and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed methods with a reasonable expectation of success. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

Matter of Record

The art made of record and not relied upon is considered pertinent to Applicant's disclosure.

Lui *et al*. teach the anti-tumor activity of oncostatin M (OM) in against breast cancer cells. (Oncostatin M inhibits breast cancer cell growth, Proceedings of the

American Association for Cancer Research Annual Meeting, (1995) Vol. 36, No. 0, pp.256. Meeting Info: Eighty-sixth Annual Meeting of the American Association for Cancer Research Toronto, Ontario, Canada March 18-22, 1995).

Breast cancer cell lines were established from solid tumors or malignant effusions removed from patients. Lui states that cellular proliferation assays indicated that the growth of 5 out of 7 cell lines were inhibited by 60-80% compared with untreated cells by picomolar concentrations of OM. The effects of OM on anchorage-independent cell lines and growth in soft agar was also examined. Lui states that OM may have broad anti-tumor activity against breast cancer and that the presence of specific high-affinity OM receptors on breast cancer cells is essential for OM to exert its biological function.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (703) 305-6915. The examiner can normally be reached on Mondays-Fridays 8:00 a.m. - 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

RMD
February 13, 2003